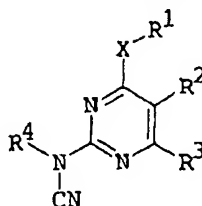


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## FUNGICIDAL 5-PHENYL SUBSTITUTED 2-(CYANOAMINO) PYRIMIDINES

The present invention relates to pyrimidines of formula I



in which

R<sup>1</sup> represents hydrogen or

15 C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>1</sub>-C<sub>10</sub>-haloalkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl, C<sub>2</sub>-C<sub>6</sub>-alkynyl, C<sub>4</sub>-C<sub>8</sub>-alkadienyl, C<sub>1</sub>-C<sub>10</sub>-alkoxy, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, phenyl, or

5- or 6-membered heteroaryl or 5- or 6-membered heterocyclyl, containing one to four nitrogen atoms or one to three  
20 nitrogen atoms and one sulfur or oxygen atom, or

tri-C<sub>1</sub>-C<sub>6</sub>-alkyl-silyl, formyl or C<sub>1</sub>-C<sub>10</sub>-alkoxycarbonyl;

wherein R<sup>1</sup> groups are unsubstituted or substituted by one to  
25 three groups R<sup>a</sup>

R<sup>a</sup> halogen, nitro, cyano, hydroxy or

30 C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkenyl, C<sub>1</sub>-C<sub>10</sub>-haloalkyl, C<sub>3</sub>-C<sub>6</sub>-halocycloalkyl, C<sub>1</sub>-C<sub>10</sub>-alkoxy, C<sub>1</sub>-C<sub>10</sub>-haloalkoxy, C<sub>1</sub>-C<sub>10</sub>-haloalkoxy, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, tri-C<sub>1</sub>-C<sub>4</sub>-alkylsilyl, phenyl, halo- or dihalo-phenyl or 5- or 6-membered heteroaryl, containing one to four  
35 nitrogen atoms or one to three nitrogen atoms and one sulfur or oxygen atom;

R<sup>2</sup> represents phenyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl or 5- or 6-membered heteroaryl, containing one to four nitrogen atoms or one to three nitrogen atoms and one sulfur or oxygen atom, which are  
40 unsubstituted or substituted by one to three groups R<sup>a</sup>;

R<sup>3</sup> represents hydrogen, halogen or

45 C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>1</sub>-C<sub>10</sub>-alkoxy, C<sub>1</sub>-C<sub>10</sub>-alkylthio, C<sub>1</sub>-C<sub>10</sub>-alkylamino or di-C<sub>1</sub>-C<sub>10</sub>-alkylamino; which are unsubstituted or substituted by one to three groups R<sup>a</sup>;

2

R<sup>4</sup> represents hydrogen or

C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>2</sub>-C<sub>6</sub>-alkenyl or C<sub>2</sub>-C<sub>6</sub>-alkynyl; which are unsubstituted or substituted by one to three groups R<sup>a</sup>; and

5

X represents O, S, NR<sup>5</sup> or a single bond, wherein  
R<sup>5</sup> represents hydrogen or C<sub>1</sub>-C<sub>10</sub>-alkyl; or

R<sup>1</sup> and R<sup>5</sup> together with the interjacent nitrogen atom form a  
10 heterocyclic ring.

Moreover, the invention relates to processes and intermediates  
for preparing these compounds, to compositions comprising them  
and to their use for controlling harmful fungi.

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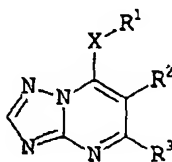
In Vestn. Slov. Kem. Drus. (1986), 33(3), 353-66 (ISSN:  
0560-3110, CAN 107:39701) it is disclosed that the reaction of  
N-pyrimid-2-ylformamide oximes with N,N-dimethylformamide diethyl  
acetal yields 2-(N-cyano-N-ethylamino)pyrimidines. In J. Org.  
20 Chem. 39 (9) 1256-1252 (1974) N-glycosylated 2-(N-cyanoamino) py-  
rimidines are disclosed and in US 4,711,959 a process for the  
preparation of 2-(N-cyanoamino) pyrimidines is described.

It is an object of the present invention to provide fungicidal  
25 compounds having improved activity.

We have found that this object is achieved by the compounds defi-  
ned at the outset. Furthermore, we have found processes for their  
preparation, compositions comprising them and methods for con-  
30 trolling harmful fungi using the compounds I.

Compounds of formula I wherein R<sup>4</sup> is an optionally substituted  
alkyl, alkenyl or alkynyl group as defined above may be obtained  
by treating a compound of the formula II

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II

40

in which R<sup>1</sup> through R<sup>3</sup> and X are as defined in formula I; with a  
strong base and an alkylation agent of formula III

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R<sup>4</sup>-Y

III

## 3

in which R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkenyl or C<sub>1</sub>-C<sub>6</sub>-alkynyl; which are unsubstituted or substituted by one to three groups R<sup>a</sup>, and Y represents a nucleophilic replaceable leaving group, preferably a halogen atom, in particular a iodine atom.

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Compounds of formula II are known for example from US 5,593,996, WO-A 98/46608, FR-A 2,765,875, WO-A 99/41255 or WO-A 99/48893.

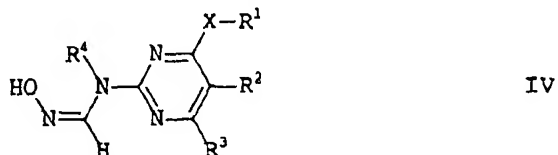
The reaction between the triazolopyrimidines of formula II, the strong base and the alkylation agent of formula III is preferably carried out in the presence of an inert solvent. Suitable solvents include ethers, such as dioxane, diethyl ether and tetrahydrofuran, halogenated hydrocarbons such as dichloromethane, amides, such as dimethylformamide or N-methylpyrrolidone and aromatic hydrocarbons, for example toluene or mixtures of these solvents. The reaction is suitably carried out at a temperature in the range from -78 °C to 100 °C, the preferred reaction temperature is from 10 °C to 80 °C, particular at ambient temperature.

20

Suitable strong bases include metal hydrides, such as sodium hydride, potassium hydride or calcium hydride, and metal amides, such as sodium amide, potassium amide, lithium diisopropylamide or potassium hexamethyldisilazide, and metal alkanes such as methyllithium, n-butyllithium or tert-butyllithium.

Furthermore, the compounds of formula I wherein R<sup>4</sup> is an optionally substituted alkyl, alkenyl or alkynyl group may be prepared by reacting a N-pyrimid-2-ylformamide oxime of formula IV

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in which R<sup>1</sup> through R<sup>3</sup> and X are as defined in formula I; with a N,N-dimethylformamide dialkyl acetate of formula V



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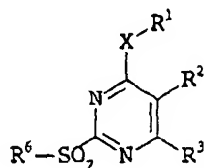
in which R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkenyl or C<sub>1</sub>-C<sub>6</sub>-alkynyl; which are unsubstituted or substituted by one to three groups R<sup>a</sup>.

The reaction between the compounds of formula IV and the compounds of formula V can be carried out analogously to the reaction described in Vestn. Slov. Kem. Drus. (1986), 33(3), 353-66.

4

Compounds of formula I wherein R<sup>4</sup> is hydrogen can preferably be prepared by treating sulfones of formula VI

5



VI

in which R<sup>1</sup> through R<sup>3</sup> and X are as defined in formula I and R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>6</sub>-haloalkyl; with cyanamide or with a metal salt of cyanamide. The use of a base and/or a solvent can be advantageous.

This process is preferably carried out in the presence of an inert solvent. Suitable solvents include aromatic hydrocarbons, such as, for example toluene or xylene, chlorinated hydrocarbons, such as, for example methylene chloride, chloroform, a chlorobenzene, ketones, such as, for example acetone, methyl ethyl ketone, methyl isopropyl ketone or methyl isobutyl ketone, nitriles, such as, for example acetonitrile or propionitrile ethers, such as, for example diethyl ether, diisopropyl ether, methyl tert-butylether, dimethoxyethane, tetrahydrofuran or dioxane, amides, such as, for example, dimethylacetamide or diethylacetamide, sulfoxides, such as, for example dimethylsulfoxide or sulfolane, or mixtures thereof.

The use of a base can be advantageous in this reaction. Suitable bases include alkali metal hydrides and earth alkaline metal hydrides, such as, for example, sodium, potassium or calcium hydrides, alkali metal hydroxides and alkaline earth metal hydroxides, such as, for example, sodium, potassium or calcium hydroxides, alkali metal carbonates and alkaline earth metal carbonates, such as, for example sodium carbonate, potassium carbonate or calcium carbonate, alkali metal bicarbonates and alkaline earth metal bicarbonates, such as sodium bicarbonate, potassium bicarbonate or calcium bicarbonate, metal amides, such as, for example sodium amide, potassium amide, lithium diisopropylamide or potassium hexamethyldisilazide, metal alkanes, such as for example methyl lithium, n-butyl lithium or tert-butyl lithium or aprotic amines, such as, for example pyridine, tributylamine, N,N-dimethylbenzylamine or diazobicycloundecene.

Various qualities of cyanamide may be employed for the process. The use of an aqueous solution of cyanamide may be preferred for practical reasons. The use of metal salts of cyanamide, potassium cyanamide, dipotassium cyanamide or calcium cyanamide is also possible.

## 5

Dependant on the used cyanamide or salt of, cyanamide and dependant on the base an appropriate solvent is employed.

The reaction is suitable carried out at a temperature in the range from -78°C to reflux temperature, the preferred reaction temperature is from 0°C to 150°C, particular at ambient temperature.

In general 1 to 3 equivalents, preferably 1.5 to 2.5 equivalents of base are employed per equivalent of sulfone of the formula VI.

Generally 2 to 6 equivalents, preferably 3 to 5 equivalents of cyanamide or salt of cyanamide are employed per equivalent of the sulfone of the general formula VI.

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Compounds of formula I wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkenyl or C<sub>1</sub>-C<sub>6</sub>-alkynyl which are unsubstituted or substituted by one to three groups R<sup>a</sup> may be prepared by alkylation of compounds of formula I wherein R<sup>4</sup> is hydrogen with an alkylation agent of formula III.

20

The use of a base can be advantageous in this reaction. Suitable bases include alkali metal hydrides and earth alkaline metal hydrides, such as, for example, sodium, potassium or calcium hydrides, alkali metal hydroxides and alkaline earth metal hydroxides, such as, for example, sodium, potassium or calcium hydroxides, alkali metal carbonates and alkaline earth metal carbonates, such as, for example sodium carbonate, potassium carbonate or calcium carbonate, alkali metal bicarbonates and alkaline earth metal bicarbonates, such as sodium bicarbonate, potassium bicarbonate or calcium bicarbonate, metal amides, such as, for example sodium amide, potassium amide, lithium diisopropylamide or potassium hexamethyldisilazide, metal alkanes, such as for example methyl lithium, n-butyl lithium or tert-butyl lithium or aprotic amines, such as, for example pyridine, tributylamine, N,N-dimethylbenzylamine or diazobicycloundecene.

The alkylation is preferably carried out in the presence of an inert solvent. Suitable solvents include aromatic hydrocarbons, such as, for example toluene or xylene, chlorinated hydrocarbons, such as, for example methylene chloride, chloroform, a chlorobenzene, ketones, such as, for example acetone, methyl ethyl ketone, methyl isopropyl ketone or methyl isobutyl ketone, nitriles, such as, for example acetonitrile or propionitrile ethers, such as, for example diethyl ether, diisopropyl ether, methyl tert-butylether, dimethoxyethane, tetrahydrofuran or dioxane, amides, such as, for example, dimethylacetamide or diethylacetamide, sulfoxi-

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des, such as, for example dimethylsulfoxide or sulfolane, or mixtures thereof.

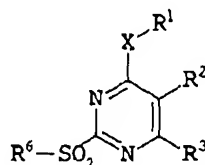
The reaction is suitably carried out at a temperature in the range from -78°C to reflux temperature, the preferred reaction temperature is 0°C to 150°C, particular ambient temperature.

In general 0.8 to 5 equivalents, preferably 0.8 to 4.5 equivalents of the alkylation agent of the formula III are employed per equivalent of the compound of formula I.

Usually 0.8 to 3 equivalents, preferably 0.8 to 2.5 equivalents of base are employed per equivalent of the compound of formula I.

It is also possible to prepare compounds of formula I wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkenyl or C<sub>1</sub>-C<sub>6</sub>-alkynyl which are unsubstituted or substituted by one to three groups R<sup>a</sup> by reacting a sulfone of formula VI

20



VI

in which R<sup>1</sup> through R<sup>3</sup> and X are as defined in formula I and R<sup>6</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>6</sub>-haloalkyl; with an alkylated cyanamide of formula VII

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VII

wherein R<sup>4</sup> is C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>6</sub>-alkenyl or C<sub>1</sub>-C<sub>6</sub>-alkynyl which are unsubstituted or substituted by one to three groups R<sup>a</sup>. The use of a base and/or a solvent can be advantageous.

35

Suitable bases and solvents are such as listed at the reaction with cyanamide.

The reaction is suitable carried out at a temperature in the range of from -78°C to reflux temperature, the preferred reaction temperature is from 0°C to 150°C, particular at ambient temperature.

The reaction is in general carried out under usual pressure.

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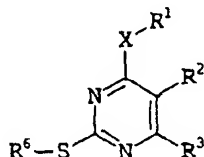
In general 1 to 3 equivalents preferably 1.5 to 2.5 equivalents of base are employed per equivalent of the sulfone of formula VI.

7

Usually 2 to 6 equivalents, preferably 3 to 5 equivalents of alkylated cyanamide of formula VII are employed per equivalents of the sulfone of formula VI.

- 5 Sulfones of the formula VI are obtained by reacting 2-thiopyrimidinederivatives of the formula VIII

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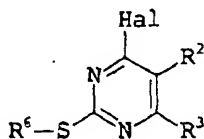
VIII

in which the variables are as defined in formula VI; with oxidizing agents, such as, for example m-chloroperbenzoic acid, per  
15 acetic acid, trifluoro per acetic acid, chlorine water, hypochlorous acid or metal salt solutions thereof in water or hydrogen peroxide, if appropriate in presence of a catalyst, such as for example wolframate.

- 20 If appropriate solvents, such as for example, methylene chloride, chloroform, carbontetrachloride, 1,2-dichloroethane or chlorobenzene are used at temperatures of -20°C to reflux.

The 2-thiopyrimidine derivatives of the formula VIII may be obtained when 6-halo-2-thiopyrimidines of formula IX

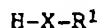
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IX

in which the substituents are as before mentioned and "Hal" denotes halogen; are reacted with a nucleophile of formula X

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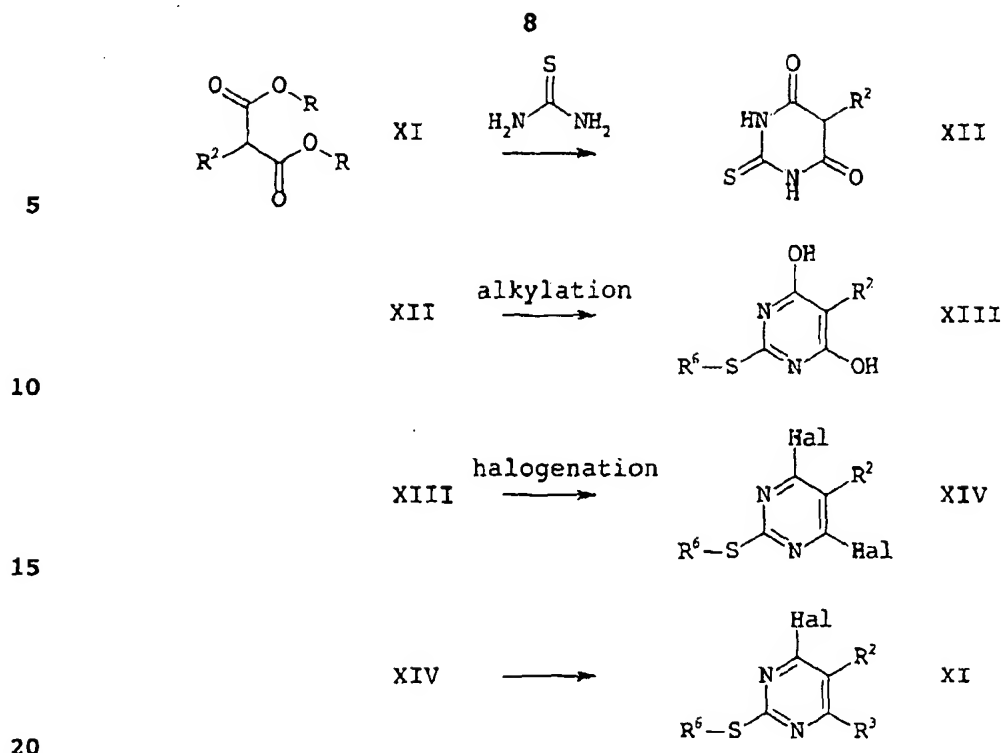


X

wherein R<sup>1</sup> and X are as defined in formula I, if appropriate in the presence of a suitable base and if appropriate in an organic  
40 solvent. The solvents and bases employed are similar to those mentioned for the preparation of the compounds of formula I.

6-halo-2-thiopyrimidines of formula IX are known in the art or may be prepared according following reaction sequence:

45



(R<sup>2</sup>, R<sup>3</sup> and R<sup>6</sup> are as defined above and R is an alkyl group) The reaction conditions are in general known in the art.

Base catalyzed reaction of dialkylmalonate with thiourea affords 2-thiobarbituric acid XII which may be selectively alkylated on sulfur to yield XIII.

Halogenation, preferably chlorination or bromination, especially chlorination, with for exaple phosphorous oxychloride or phosphorous oxybromide in the presence of a tertiary amine base then affords the dihalo derivative XIV.

Subsequent introduction of the radical R<sup>3</sup>, if appropriate, via nucleophilic substitution affords the 6-halo-2-thiopyrimidine of formula IX.

Sulfones of formula VI and 2-thiopyrimidine derivatives of formula VIII are novel.

In the symbol definitions given in the formulae above, collective terms were used which generally represent the following substituents:

- halogen: fluorine, chlorine, bromine and iodine;

- C<sub>1</sub>-C<sub>6</sub>-alkyl and the alkyl moieties of C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>1</sub>-C<sub>6</sub>-alkylthio, C<sub>1</sub>-C<sub>6</sub>-alkylamino, di-C<sub>1</sub>-C<sub>6</sub>-alkylamine or



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C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl: saturated, straight-chain or branched hydrocarbon radicals having 1 to 6 carbon atoms, preferably C<sub>1</sub>-C<sub>4</sub>-alkyl, such as methyl, ethyl, propyl, 1-methylethyl, butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl; or pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 2,2-di-methylpropyl, 1-ethylpropyl, hexyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2-dimethylbutyl, 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl; preferably ethyl or methyl;

- C<sub>1</sub>-C<sub>6</sub>-haloalkyl and the haloalkyl moieties of C<sub>1</sub>-C<sub>6</sub>-haloalkoxy:  
15 straight-chain or branched alkyl groups having 1 to 6 carbon atoms (as mentioned above), where the hydrogen atoms in these groups may be partially or fully replaced by halogen atoms as mentioned above, for example C<sub>1</sub>-C<sub>2</sub>-haloalkyl, such as chloromethyl, bromomethyl, dichloromethyl, trichloromethyl, 20 fluoromethyl, difluoromethyl, trifluoromethyl, chlorofluoromethyl, dichlorofluoromethyl, chlorodifluoromethyl, 1-chloroethyl, 1-bromoethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2-chloro-2-fluoroethyl, 2-chloro-2,2-difluoroethyl, 2,2-dichloro-2-fluoroethyl, 25 2,2,2-trichloroethyl and pentafluoroethyl; preferably 2,2,2-trifluoroethyl or 1,1,1-trifluoroprop-2-yl;

- C<sub>3</sub>-C<sub>8</sub>-cycloalkyl: monocyclic, saturated hydrocarbon radicals having 3 to 6 or 8 carbon ring members, for example cyclopropyl, 30 cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably 5 to 7 carbon atoms, in particular cyclopentyl being optionally substituted by one or more halogen atoms, nitro, cyano, C<sub>1</sub>-C<sub>6</sub>-alkyl or C<sub>1</sub>-C<sub>6</sub>-alkoxy.

35 - C<sub>2</sub>-C<sub>4</sub>-alkenyl: unsaturated, straight-chain or branched hydrocarbon radicals having 2 to 4 carbon atoms and a double bond in any position, for example ethenyl, 1-propenyl, 2-propenyl, 1-methylethenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-methyl-1-propenyl, 2-methyl-1-propenyl, 1-methyl-2-propenyl and 40 2-methyl-2-propenyl; preferably allyl or 2-methylallyl.

- C<sub>2</sub>-C<sub>4</sub>-haloalkenyl and the haloalkenyl moieties of C<sub>2</sub>-C<sub>4</sub>-haloalkenyloxy: unsaturated, straight-chain or branched hydrocarbon radicals having 2 to 4 carbon atoms and a double bond 45 in any position (as mentioned above), where the hydrogen atoms in these groups may be partially or fully replaced by halogen atoms

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as mentioned above, in particular by fluorine, chlorine and bromine;

- C<sub>2</sub>-C<sub>4</sub>-alkynyl: straight-chain or branched hydrocarbon radicals  
5 having 3 to 4 carbon atoms and a triple bond in any position, for example ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne and 1-methyl-2-propynyl;

- C<sub>3</sub>-C<sub>4</sub>-haloalkynyl and the haloalkynyl moieties of  
10 C<sub>2</sub>-C<sub>4</sub>-haloalkynyloxy: unsaturated, straight-chain or branched hydrocarbon radicals having 2 to 4 carbon atoms and a triple bond in any position (as mentioned above), where the hydrogen atoms in these groups may be partially or fully replaced by halogen atoms as mentioned above, in particular by fluorine, chlorine and  
15 bromine;

5-membered heteroaryl, containing one to four nitrogen atoms or one to three nitrogen atoms and one sulfur or oxygen atom: 5-membered heteroaryl groups which, in addition to carbon atoms, may  
20 contain one to four nitrogen atoms or one to three nitrogen atoms and one sulfur or oxygen atom as ring members, for example 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyrrolyl, 3-pyrrolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 3-isothiazolyl, 4-isothiazolyl, 5-isothiazolyl, 3-pyrazolyl, 4-pyrazolyl, 5-pyrazolyl,  
25 2-oxazolyl, 4-oxazolyl, 5-oxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-imidazolyl, 4-imidazolyl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,4-triazol-3-yl, 1,3,4-oxadiazol-2-yl, 1,3,4-thiadiazol-2-yl and 1,3,4-triazol-2-yl;

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6-membered heteroaryl, containing one to four nitrogen atoms: 6-membered heteroaryl groups which, in addition to carbon atoms, may contain one to three or one to four nitrogen atoms as ring members, for example 2-pyridinyl, 3-pyridinyl, 4-pyridinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 1,3,5-triazin-2-yl and 1,2,4-triazin-3-yl; preferred hetaryl moieties are pyridyl, pyrimidyl, pyrazolyl or thienyl.

40 5- or 6-membered heterocyclyl, containing one to four nitrogen atoms or one to three nitrogen atoms and one sulfur or oxygen atom, for example 2-tetrahydrofuranyl, 3-tetrahydrofuranyl, 2-tetrahydrothienyl, 3-tetrahydrothienyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 3-isoxazolidinyl, 4-isoxazolidinyl, 5-isoxazolidinyl,  
45 3-isothiazolidinyl, 4-isothiazolidinyl, 5-isothiazolidinyl, 3-pyrazolidinyl, 4-pyrazolidinyl, 5-pyrazolidinyl, 2-oxazolidinyl, 4-oxazolidinyl, 5-oxazolidinyl, 2-thiazolidinyl, 4-thiazolidinyl,

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5-thiazolidinyl, 2-imidazolidinyl, 4-imidazolidinyl, 1,2,4-oxadiazolidin-3-yl, 1,2,4-oxadiazolidin-5-yl, 1,2,4-thiadiazolidin-3-yl, 1,2,4-thiadiazolidin-5-yl, 1,2,4-triazolidin-3-yl, 1,3,4-oxadiazolidin-2-yl, 1,3,4-thiadiazolidin-2-yl, 1,3,4-triazolidin-2-yl, 2,3-dihydrofur-2-yl, 2,3-dihydrofur-3-yl, 2,4-dihydrofur-2-yl, 2,4-dihydrofur-3-yl, 2,3-dihydrothien-2-yl, 2,3-dihydrothien-3-yl, 2,4-dihydrothien-2-yl, 2,4-dihydrothien-3-yl, 2-pyrrolin-2-yl, 2-pyrrolin-3-yl, 3-pyrrolin-2-yl, 3-pyrrolin-3-yl, 2-isoxazolin-3-yl, 3-isoxazolin-3-yl, 4-isoxazolin-3-yl, 2-isoxazolin-4-yl, 3-isoxazolin-4-yl, 4-isoxazolin-4-yl, 2-isoxazolin-5-yl, 3-isoxazolin-5-yl, 4-isoxazolin-5-yl, 2-isothiazolin-3-yl, 3-isothiazolin-3-yl, 4-isothiazolin-3-yl, 2-isothiazolin-4-yl, 3-isothiazolin-4-yl, 4-isothiazolin-4-yl, 2-isothiazolin-5-yl, 3-isothiazolin-5-yl, 4-isothiazolin-5-yl, 2,3-dihydropyrazol-1-yl, 2,3-dihydropyrazol-2-yl, 2,3-dihydropyrazol-3-yl, 2,3-dihydropyrazol-4-yl, 2,3-dihydropyrazol-5-yl, 3,4-dihydropyrazol-1-yl, 3,4-dihydropyrazol-3-yl, 3,4-dihydropyrazol-4-yl, 3,4-dihydropyrazol-5-yl, 4,5-dihydropyrazol-1-yl, 4,5-dihydropyrazol-3-yl, 4,5-dihydropyrazol-4-yl, 4,5-dihydropyrazol-5-yl, 2,3-dihydrooxazol-2-yl, 2,3-dihydrooxazol-3-yl, 2,3-dihydrooxazol-4-yl, 2,3-dihydrooxazol-5-yl, 3,4-dihydrooxazol-2-yl, 3,4-dihydrooxazol-3-yl, 3,4-dihydrooxazol-4-yl, 3,4-dihydrooxazol-5-yl, 3,4-dihydrooxazol-2-yl, 3,4-dihydrooxazol-3-yl, 3,4-dihydrooxazol-4-yl, 2-piperidinyl, 3-piperidinyl, 4-piperidinyl, 1,3-dioxan-5-yl, 2-tetrahydropyranyl, 4-tetrahydropyranyl, 2-tetrahydrothienyl, 3-hexahydropyridazinyl, 4-hexahydropyridazinyl, 2-hexahydropyrimidinyl, 4-hexahydropyrimidinyl, 5-hexahydropyrimidinyl, 2-piperazinyl, 1,3,5-hexahydro-triazin-2-yl and 1,2,4-hexahydrotriazin-3-yl; preferred heterocyclyl groups are pyrrolidinyl, pyrazolidinyl, piperidinyl, piperazinyl or morpholin-4-yl.

The particularly preferred embodiments of the intermediates with respect to the variables correspond to those of the radicals R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> of formula I.

With respect to their intended use, preference is given to pyrimidines of formula I having the following substituents, where the preference is valid in each case on its own or in combination:

Compounds of formula I are preferred wherein R<sup>1</sup> denotes C<sub>3</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl-C<sub>1</sub>-C<sub>6</sub>-alkyl, C<sub>1</sub>-C<sub>10</sub>-haloalkyl or phenyl being optionally substituted by one to three halogen atoms or C<sub>1</sub>-C<sub>10</sub>-alkyl or C<sub>1</sub>-C<sub>10</sub>-alkoxy.

## 12

Furthermore, particular preference is given to compounds I in which  $R^1$  is  $C_1$ - $C_{10}$ -haloalkyl, preferably polyfluorinated alkyl, in particular 2,2,2-trifluoroethyl, 2-(1,1,1-trifluoropropyl) or 2-(1,1,1-trifluorobutyl).

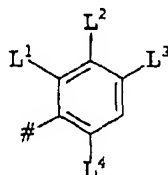
5

Likewise, particular preference is given to compounds I in which  $R^1$  denotes optionally substituted  $C_3$ - $C_8$ -cycloalkyl, preferably cyclopentyl or cyclohexyl.

- 10 Moreover, particular preference is given to compounds I in which  $R^2$  represents phenyl being substituted by 2 or 3 substituents. Most preferred at least one of these substituents is attached in the 2-position with respect to the point of attachment to the pyrimidine moiety. Such substituents preferably include halogen
- 15 or alkoxy.

Furthermore, particular preference is given to compounds I in which  $R^2$  represents a phenyl group of formula

20



- 25 wherein  $L^1$  through  $L^4$  each independently represent hydrogen, fluorine, chlorine or methoxy, in particular  $L^1$  represents fluorine or chlorine,  $L^2$  and  $L^4$  each independently represent hydrogen, fluorine or chlorine, and  $L^3$  represents hydrogen, fluorine, chlorine or methoxy.

30

Particular preference is given to compounds of formula I in which  $R^3$  is chlorine.

- Besides, particular preference is given to compounds I in which  $R^4$
- 35 represents hydrogen,  $C_1$ - $C_6$ -alkyl,  $C_2$ - $C_6$ -alkenyl or  $C_2$ - $C_6$ -alkynyl; or phenyl- $C_1$ - $C_4$ -alkyl, wherein the phenyl ring may be substituted by one or two halogen atoms.

- Likewise, particular preference is given to compounds I in which
- 40  $R^4$  is hydrogen,  $C_1$ - $C_6$ -alkyl or benzyl, especially  $C_1$ - $C_6$ -alkyl.

Particular preference is given to compounds I in which X is  $NR^5$  and  $R^5$  is hydrogen,  $C_1$ - $C_{10}$ -alkyl or  $C_1$ - $C_{10}$ -haloalkyl, in particular hydrogen.

45

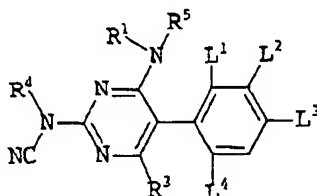
Besides, particular preference is given to compounds I in which  $R^5$  represents  $C_1$ - $C_6$ -alkyl, especially hydrogen or methyl.

13

Particular preference is also given to compounds I in which X represent  $\text{NR}^5$  and  $\text{R}^1$  together with the interjacent nitrogen atom form an optionally substituted heterocyclic ring, preferably an optionally substituted 3- to 7-membered heterocyclic ring, in particular a pyrrolidine, piperidine, tetrahydropyridine, in particular 1,2,3,6-tetrahydropyridine or azepane ring which is optionally substituted by one or more  $\text{C}_1$ - $\text{C}_{10}$ -alkyl groups.

Most preferred are the compounds of formula IA

10



IA

15

in which  $\text{R}^1$  to  $\text{R}^5$  have the meaning given in formula I,  $\text{L}^1$  is F or Cl,  $\text{L}^2$  and  $\text{L}^4$  each independently are H, F or Cl, and  $\text{L}^3$  is H, F, Cl or  $\text{OCH}_3$ .

20 Likewise, most preferred are the compounds wherein  $\text{R}^3$  is chlorine, X is NH,  $\text{R}^4$  is  $\text{C}_1$ - $\text{C}_6$ -alkyl,  $\text{C}_2$ - $\text{C}_6$ -alkenyl or  $\text{C}_2$ - $\text{C}_6$ -alkynyl, especially  $\text{C}_1$ - $\text{C}_6$ -alkyl,  $\text{R}^2$  represents phenyl optionally substituted by one or more fluorine and/or chlorine atoms and/or methoxy groups.

25 Particularly preferred are following compounds of formula IA:

	$\text{R}^1$	$\text{R}^5$	$\text{R}^3$	$\text{R}^4$	$\text{L}^1$	$\text{L}^2$	$\text{L}^3$	$\text{L}^4$
	$\text{CH}(\text{CH}_3)\text{CF}_3$	H	Cl	$\text{CH}_3$	F	H	F	F
	$\text{CH}(\text{CH}_3)\text{CF}_3$	H	Cl	$(\text{CH}_2)_3\text{CH}_3$	F	H	F	F
30	$\text{CH}(\text{CH}_3)_2$	H	Cl	$\text{CH}_3$	F	H	F	F
	$\text{c-C}_3\text{H}_5$	H	Cl	$\text{CH}_3$	F	F	H	F
	azepan-1-yl	H	Cl	$\text{CH}_3$	H	F	H	F
	$(\text{CH}_2)_2\text{CH}(\text{CH}_3)(\text{CH}_2)_2$		Cl	$\text{CH}_3$	F	H	H	Cl
35	$\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$	H	Cl	$\text{CH}_3$	F	H	H	Cl
	$(\text{CH}_2)_2\text{CH}(\text{CH}_3)(\text{CH}_2)_2$		Cl	$\text{CH}_3$	F	H	F	F
	$\text{CH}(\text{CH}_3)\text{CF}_3$	H	Cl	$\text{CH}_3$	F	H	F	F

Included in the scope of the present Invention are (R) and (S) isomers of compounds of general formula I having a chiral center and the racemates thereof, and salts, N-Oxides and acid addition compounds.

The compounds according to formula I are superior through their valuable fungicidal properties, in particular their enhanced systemicity. For example, they can be used in agriculture or related fields for the control of phytopathogenic fungi such as

## 14

*Alternaria solani*, *Botrytis cinerea*, *Cercospora beticola*, *Cladosporium herbarum*, *Corticium rolfii*, *Erysiphe graminis*, *Helminthosporium tritici repentis*, *Lepidosphaeria nodorum*, *Micronectriella nivalis*, *Monilinia fructigena*, *Mycosphaerella ligulicola*, *Mycosphaerella pinodes*, *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, *Uncinula necator* and *Venturia inaequalis*, in particular *Pyricularia oryzae*, *Rhizoctonia solani* and *Venturia inaequalis*. The compounds of formula I according to the invention possess a high fungicidal activity within a wide concentration range.

Due to excellent activity, the compounds of formula I may be used in cultivation of all plants where infection by phytopathogenic fungi is not desired, e.g. cereals, solanaceous crops, vegetables, legumes, apples, vine.

The Invention further provides a fungicidal composition which comprises an active ingredient, which is at least one compound of formula I as defined above, and one or more carriers. A method of making such a composition is also provided which comprises bringing a compound of formula I as defined above into association with the carrier(s). Such a composition may contain a single active ingredient or a mixture of several active ingredients of the present Invention. It is also envisaged that different isomers or mixtures of isomers may have different levels or spectra of activity and thus compositions may comprise individual isomers or mixtures of isomers.

A composition according to the Invention preferably contains from 0.5% to 95% by weight (w/w) of active ingredient.

A carrier in a composition according to the Invention is any material with which the active ingredient is formulated to facilitate application to the locus to be treated, which may for example be a plant, seed, soil, or water in which a plant grows, or to facilitate storage, transport or handling. A carrier may be a solid or a liquid, including material which is normally a gas but which has been compressed to form a liquid.

The compositions may be manufactured into e.g. emulsion concentrates, solutions, oil in water emulsions, wettable powders, soluble powders, suspension concentrates, dusts, granules, water dispersible granules, micro-capsules, gels, tablets and other formulation types by well-established procedures. These procedures include intensive mixing and/or milling of the active ingredients with other substances, such as fillers, solvents, solid carriers, surface active compounds (surfactants), and optionally solid and/

## 15

or liquid auxiliaries and/or adjuvants. The form of application such as spraying, atomizing, dispersing or pouring may be Chosen like the compositions according to the desired objectives and the given circumstances.

5

Solvents may be aromatic hydrocarbons, e.g. Solvess® 200, substituted naphthalenes, phthalic acid esters, such as dibutyl or dioctyl phthalate, aliphatic hydrocarbons, e.g. cyclohexane or Paraffins, alcohols and glycols as well as their ethers and

- 10 esters, e.g. ethanol, ethyleneglycol mono- and dimethyl ether, ketones such as cyclohexanone, strongly polar solvents such as N-methyl-2-pyrrolidone, or  $\gamma$ -butyrolactone, higher alkyl pyrrolidones, e.g. n-octylpyrrolidone or cyclohexylpyrrolidone, epoxidized plant oil esters, e.g. methylated coconut or soybean oil ester  
15 and watet. Mixtures of different liquids are offen suitable.

Solid carriers, which may be used for dusts, wettable powders, watet dispersible granules, or granules, may be mineral fillers, such as calcite, talc, kaolin, montmorillonite or attapulgite.

- 20 The physical properties may be improved by addition of highly dispersed silica gel or Polymers. Carriers for granules may be porous material, e.g. pumice, kaolin, sepiolite, bentonite; non-sorptive carriers may be calcite or sand. Additionally, a multitude of pregranulated inorganic or organic materials may be used,  
25 such as dolomite or crushed plant residues.

Pesticidal compositions are often formulated and transported in a concentrated form which is subsequently diluted by the user before application. The presence of small amounts of a carrier  
30 which is a surfactant facilitates this process of dilution. Thus, preferably at least one carrier in a composition according to the Invention is a surfactant. For example, the composition may contain at two or more carriers, at least one of which is a surfactant.

35

Surfactants may be nonionic, anionic, cationic or zwitterionic substances with good dispersing, emulsifying and wetting properties depending an the nature of the compound according to general formula I to be formulated. Surfactants may also mean  
40 mixtures of individual surfactants.

The compositions of the Invention may for example be formulated as wettable powders, water dispersible granules, dusts, granules, tablets, solutions, emulsifiable concentrates, emulsions,

- 45 suspension concentrates and aerosols. Wettable powders usually contain 5 to 90% w/w of active ingredient and usually contain in addition to solid inert carrier, 3 to 10% w/w of dispersing and

## 16

wetting agents and, where necessary, 0 to 10% w/w of stabilizer(s) and/or other additives such as penetrants or stickers. Dusts are usually formulated as a dust concentrate having a similar composition to that of a wettable powder but without a dispersant, and may be diluted in the field with further solid carrier to give a composition usually containing 0.5 to 10% w/w of active ingredient. Water dispersible granules and granules are usually prepared to have a size between 0.15 mm and 2.0 mm and may be manufactured by a variety of techniques. Generally, these types of granules will contain 0.5 to 90% w/w active ingredient and 0 to 20% w/w of additives such as stabilizer, surfactants, slow release modifiers and binding agents. The so-called "dry flowables" consist of relatively small granules having a relatively high concentration of active ingredient. Emulsifiable concentrates usually contain, in addition to a solvent or a mixture of solvents, 1 to 80% w/v active ingredient, 2 to 20% w/v emulsifiers and 0 to 20% w/v of other additives such as stabilizers, penetrants and corrosion inhibitors. Suspension concentrates are usually milled so as to obtain a stable, nonsedimenting flowable product and usually contain 5 to 75% w/v active ingredient, 0.5 to 15% w/v of dispersing agents, 0.1 to 10% w/v of suspending agents such as protective colloids and thixotropic agents, 0 to 10% w/v of other additives such as defoamers, corrosion inhibitors, stabilizers, penetrants and stickers, and water or an organic liquid in which the active ingredient is substantially insoluble; certain organic solids or inorganic salts may be present dissolved in the formulation to assist in preventing sedimentation and crystallization or as antifreeze agents for water. Aqueous dispersions and emulsions, for example compositions obtained by diluting the formulated product according to the Invention with water, also lie within the scope of the invention.

Of particular interest in enhancing the duration of the protective activity of the compounds of this Invention is the use of a carrier which will provide slow release of the pesticidal compounds into the environment of a plant which is to be protected.

The biological activity of the active ingredient can also be increased by including an adjuvant in the spray dilution. An adjuvant is defined here as a substance which can increase the biological activity of an active ingredient but is not itself significantly biologically active. The adjuvant can either be included in the formulation as a coformulant or carrier, or can be added to the spray tank together with the formulation containing the active ingredient.



## 17

As a commodity the compositions may preferably be in a concentrated form whereas the end user generally employs diluted compositions. The compositions may be diluted to a concentration down to 0.001 % of active ingredient. The doses usually are in the range 5 from 0.01 to 10 kg a.i./ha.

Examples of formulations according to the Invention are:

## Emulsion Concentrate (EC)

10

Active Ingredient	Compound of Example 5	30 % (w/v)
Emulsifier(s)	Atlox® 4856 B/Atlox® 4858 B <sup>1)</sup> (mixture containing calcium alkyl aryl sulfonate, fatty alcohol ethoxylates and light aromatics/mixture containing calcium alkyl aryl sulfonate, fatty alcohol ethoxylates and light aromatics)	5 % (w/v)
20 Solvent	Shellsol® A <sup>2)</sup> (mixture of C <sub>9</sub> -C <sub>10</sub> -aromatic hydrocarbons)	to 1000 ml

## Suspension Concentrate (SC)

25

Active Ingredient	Compound of Example 5	50 % (w/v)
Dispersing agent	Soprophor® FL <sup>3)</sup> (polyoxyethylene polyaryl phenyl ether phosphate amine salt)	3 % (w/v)
30 Antifoaming agent	Rhodorsil® 422 <sup>3)</sup> (nonionic aqueous emulsion of polydimethylsiloxanes)	0.2 (w/v)
Structure agent	Kelzan® S <sup>4)</sup> (Xanthan gum)	0.2 (w/v)
35 Antifreezing agent	Propylene glycol	5 % (w/v)
Biocidal agent	Proxel® <sup>5)</sup> (aqueous dipropylene glycol solution containing 20% 1,2-beniso- thiazolin-3-one)	0.1 (w/v)
Water		to 1000 ml

45

## 18

## Wettable Powder (WP)

Active Ingredient	Compound of Example 7	60 % (w/w)
Wetting agent	Atlox® 4995 <sup>1)</sup>	2 % (w/w)
5 (polyoxyethylene alkyl ether)		
Dispersing agent	Witcosperse® D-60 6)	3 % (w/w)
	(mixture of sodium salts of condensed naphthalene sulfonic acid and alkylaryl polyoxy acetates	
10 Carrier / Filter	Kaolin	35 % (w/w)

## Water Dispersible Granules (WG)

15 Active Ingredient	Compound of Example 7	50 % (w/w)
Dispersing /	Witcosperse® D-450 6)	8 % (w/w)
Binding agent	(mixture of sodium salts of condensed naphthalene sulfonic acid and alkyl sulfonates)	
20 Wetting agent	Morwet® EFW 6)	2 % (w/w)
	(formaldehyde condensation product) Antifoaming agent	
	Rhodorsil® EP 6703 3)	1 % (w/w)
25 (encapsulated silicone)		
Disintegrant	Agrimer® ATF')	2 % (w/w)
	(cross-linked homopolymer of N-vinyl-2 pyrrolidone)	
Carrier & Filter	Kaolin	35 % (w/w)

30

1) commercially available from ICI Surfactants

2) commercially available from Deutsche Shell AG

3) commercially available from Rhône-Poulenc

4) commercially available from Kelco Co.

35 5) commercially available from Zeneca

6) commercially available from Witco

7) commercially available from International Speciality Products

The compositions of this invention can be applied to the plants  
 40 or their environment simultaneous with or in succession with  
 other active substances. These other active substances can be Bi-  
 ther fertilisers, agents which donate trace elements or other  
 preparations which influence plant growth. However, they can also  
 be selective herbicides, insecticides, fungicides, bactericides,  
 45 nematicides, algicides, molluscicides, rodenticides, virucides,  
 compounds inducing resistance into plants, biological control  
 agents such as viruses, bacteria, nematodes, fungi and other mi-

## 19

oroorganisms, repellents of birds and animals, and plant growth regulators, or mixtures of several of these preparations, if appropriate together with other carrier substances conventionally used in the art of formulation, surfactants or other additives 5 which promote application.

Furthermore, the other pesticide can have a synergistic effect anthe pesticidal activity of the compound of formula I.

- 10 The other fungicidal compound can be, for example, one which is also capable of combating diseases of cereals (e.g. wheat) such as those caused by *Erysiphe*, *Puccinia*, *Septoria*, *Gibberella* and *Helminthosporium* spp., seed and soil Borne diseases and downy and powdery mildews an eines, early and late blight an solanaceous 15 crops, and powdery mildew and scab an apples etc. These mixtures of fungicides can have a broader spectrum of activity than the compound of general formula I alone. Furthermore, the other fungicide can have a synergistic effect an the fungicidal activities of the compound of formula I.

## 20

- Examples of the other fungicidal compounds are anilazine, azoxystrobin, benalaxyl, benomyl, binapacryl, bitertanol, blasticidin S, Bordeaux mixture, bromuconazole, bupirimate, captafol, captan, carbendazim, carboxin, carpropamid, chlorbenzthiazon, chlorothalonil, chlozolate, copper-containing compounds such as copper 25 oxychloride, and copper sulfate, cycloheximide, cymoxanil, cypofuram, cyproconazole, cyprodinil, dichlofluanid, dichlone, dichloran, diclobutrazol, diclocymet, diclomezine, diethofencarb, difenoconazole, diflumetorim, dimethirimol, dimethomorph, diniconazole, dinocap, ditalimfos, dithianon, dodemorph, dodine, edifenphos, epoxiconazole, etaconazole, ethirimol, etridiazole, famoxadone, fenapanil, fenamidone, fenarimol, fenbuconazole, fenfuram, fenhexamid, fenoxanil, fenciclonil, fenpropidin, fenpropimorph, fentin, fentin acetate, fentin hydroxide, ferimzone, fluazinam, fludioxonil, flumetover, fluquinconazole, flusilazole, flusulfamide, flutolanil, flutriafol, folpet, fosetylaluminium, fuberidazole, furalaxyl, furametpyr, guazatine, hexaconazole, IKF-916, imazalil, iminoctadine, ipconazole, iprodione, isoprothiolane, iprovalicarb, kasugamycin, KH-7281, kitazin P, 40 kresoximmethyl, mancozeb, maneb, mepanipyrim, mepronil, metalaxyl, metconazole, methfuroxam, MON 65500, myclobutanil, neoasozin, nicket dimethyldithiocarbamate, nitrothalisopropyl, nuarimol, ofurace, organo mercury compounds, oxadixyl, oxycarboxin, penconazole, pencycuron, phenazineoxide, phthalide, polyoxin D, 45 polgram, probenazole, prochloraz, procymidione, propamocarb, propiconazole, propineb, pyraclostrobin, pyrazophos, pyrifenoxy, pyrimethanil, pyroquilon, pyroxyfur, quinomethionate, quinoxifen,

## 20.

quintozene, spiroxamine, SSF-126, SSF-129, streptomycin, sulfur, tebuconazole, tecloftalame, tecnazene, tetraconazole, thiabendazole, thifluzamide, thiophanate-methyl, thiram, tolclofosmethyl, tolylfluanid, triadimefon, triadimenol, triazbutil, triazoxide, 5 tricyclazole, tridemorph, trifloxystrobin, triflumizole, triforine, triticonazole, validamycin A, vinclozolin, XRD-563, zarilamid, zineb, ziram.

In addition, the co-formulations according to the Invention may 10 contain at least one compound of formula I and any of the following classes of biological control agents such as viruses, bacteria, nematodes, fungi, and other microorganisms which are suitable to control insects, weeds or plant diseases or to induce host resistance in the plants. Examples of such biological control 15 agents are: *Bacillus thuringiensis*, *Verticillium lecanii*, *Autographa californica NPV*, *Beauveria bassiana*, *Ampelomyces quisqualis*, *Bacillus subtilis*, *Pseudomonas chlororaphis*, *Pseudomonas fluorescens*, *Streptomyces griseoviridis* and *Trichoderma harzianum*.

20 Moreover, the co-formulations according to the Invention may contain at least one compound of formula I and a chemical agent that induces the systemic acquired resistance in plants such as for example isonicotinic acid or derivatives thereof, 2,2-dichloro-3,3-dimethylcyclopropanecarboxylic acid or BION.

25 The compounds of formula I can be mixed with soil, peat or other rooting media for the protection of the plants against seed-borne, soilborne or foliar fungal diseases.

30 The Invention still further provides the use as a fungicide of a compound of the formula I as defined above or a composition as defined above, and a method for combating fungus at a locus, which comprises treating the locus, which may be for example plants subject to or subjected to fungal attack, seeds of such 35 plants or the medium in which such plants are growing or are to be grown, with such a compound or composition.

The present Invention is of wide applicability in the protection of crop and ornamental plants against fungal attack. Typical 40 crops which may be protected include cereals, grain crops such as wheat and barley, rice, sugar Beet, top fruit, peanuts, potatoes, vegetables and tomatoes. The duration of the protection is normally dependent on the individual compound selected, and also a variety of external factors, such as climate, whose impact is 45 normally mitigated by the use of a suitable formulation.

## 21

## Synthesis Examples

With due modification of the starting compounds, the protocols shown in the synthesis examples below were used for obtaining  
 5 further compounds I. The resulting compounds, together with physical data, are listed in the Tables which follow.

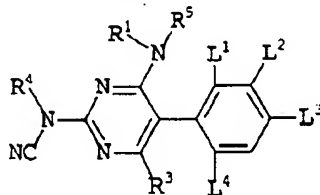
## Example 1

10 Preparation of 2-(N-cyano-N-methylamino)-4-chloro-5-(2,4,6-trifluorophenyl)-6-(1,1,1-trifluoroprop-2-ylamino)-pyrimidine

A mixture of 5-chloro-6-(2,4,6-trifluorophenyl)-7-(1,1,1-trifluoroprop-2-ylamino)-triazolo[1.5a]pyrimidine (2.5 g, 6.3 mmol, prepared according to WO-A 98/46608); dimethylformamide (15ml), sodium hydride (0.25 g, 60 %) and methyl iodide is stirred at ambient temperature for 45 minutes. The reaction mixture is poured into water (400 ml) and extracted with diethylether twice (300 ml). The organic Phase is separated, dried with anhydrous sodium  
 20 sulphate and filtered. The filtrate is evaporated under reduced Pressure and purified by flash chromatography to yield 0.2 g of the product as a colorless oil.

Examples 2-20: Table I (synthesized analogously to Ex. 1)

25



30

Ex.	R <sup>1</sup>	R <sup>5</sup>	R <sup>4</sup>	L <sup>1</sup>	L <sup>2</sup>	L <sup>3</sup>	L <sup>4</sup>	melting point (°C)
35	2	1,1,1-trifluoroprop-2-yl	H	butyl	F	H	F	168-172
	3	iso-propyl	H	methyl	F	H	F	130
	4	cyclopentyl	H	methyl	F	F	H	140
	5	-(CH <sub>2</sub> ) <sub>2</sub> -CH(CH <sub>3</sub> )-(CH <sub>2</sub> ) <sub>2</sub> -	methyl	F	H	H	Cl	oil
40	6	2-butyl	H	methyl	F	H	H	oil
	7	-(CH <sub>2</sub> ) <sub>2</sub> -CH(CH <sub>3</sub> )-(CH <sub>2</sub> ) <sub>2</sub> -	methyl	F	H	F	F	100
	8	1,1,1-trifluoroprop-2-yl	methyl	methyl	F	H	F	86
	9	but-2-yl	ethyl	methyl	F	H	F	
45	10	norborn-2-yl	H	methyl	F	H	F	
	11	-(CH <sub>2</sub> ) <sub>2</sub> -CH(CH <sub>3</sub> )-(CH <sub>2</sub> ) <sub>2</sub> -	ethyl	F	H	H	Cl	

## 22

Ex.	R <sup>1</sup>	R <sup>5</sup>	R <sup>4</sup>	L <sup>1</sup>	L <sup>2</sup>	L <sup>3</sup>	L <sup>4</sup>	melting point (°C)
5	12	cyclopentyl	H	methyl	F	H	F	F
	13	iso-propyl	H	methyl	F	H	H	Cl
	14	ethyl	ethyl	methyl	F	H	F	F
10	15	2,2,2-trifluoro-ethyl	H	methyl	F	H	F	F
	16	1,1,1-trifluoro-prop-2-yl	H	ethyl	F		H	Cl
	17	2-butyl	H	methyl	F	H	H	Cl
15	18	norborn-2-yl	H	methyl	F	H	H	Cl
	19	1,1,1-trifluoro-prop-2-yl	H	methyl	F	H	OCH <sub>3</sub>	F
	20	methallyl	ethyl	methyl	F	H	F	F
20	21	2,2,2-trifluoro-ethyl	H	allyl	F	H	H	Cl
	22	1,1,1-trifluoro-prop-2-yl	H	n-propyl	F	H	F	F
	23	-(CH <sub>2</sub> ) <sub>7</sub> -		methyl	H	F	H	F
	24	iso-propyl	ethyl	methyl	F	H	H	Cl
	25	1,1,1-trifluoro-prop-2-yl	H	methyl	F	H	F	F

25

## Example 26

## Preparation of

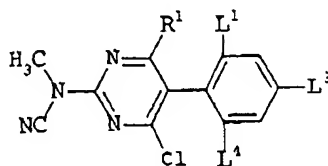
2-(N-cyano-N-methylamino)-4-chloro-5-(2,4,6-trifluorophenyl)-6-cyclohexylpyrimidine

A mixture of 5-chloro-6-(2,4,6-trifluorophenyl)-7-cyclohexyltriazolo[1.5a]pyrimidine (2.5 g, 6.3 mmol, prepared according to WO-A 99/41255), dimethylformamide (15ml), sodium hydride (0.25 g, 60 %) and methyl iodide is stirred at ambient temperature for 45 minutes. The reaction mixture is poured into water (400 ml) and extracted with diethylether twice (300 ml). The organic phase is separated, dried with anhydrous sodium sulphate and filtered. The filtrate is evaporated under reduced pressure and purified by flash chromatography to yield 0.2 g of the product as a colorless oil.

45

## 23

Examples 27-39: Table II (synthesized analogously to Ex. 26)



5

Ex.	R <sup>1</sup>	L <sup>1</sup>	L <sup>3</sup>	L <sup>4</sup>	melting point (°C)
27	n-heptyl	F	F	F	
28	cyclopentyl	F	F	F	
29	cyclohexyl	F	F	F	
30	4-methylcyclohexyl	F	F	F	
31	2-methylpropyl	F	F	F	
32	n-heptyl	F	H	Cl	
33	cyclopentyl	F	H	Cl	
34	cyclohexyl	F	H	Cl	
35	n-hexyl	F	H	Cl	
36	4-methylcyclohexyl	F	H	Cl	
37	2-methylpropyl	F	H	Cl	
38	4-fluorocyclohexyl	F	F	F	
39	4-fluorocyclohexyl	F	OCH <sub>3</sub>	F	

## Example 40

30 Preparation of  
4-chloro-2-(N-cyanoamino)-6-[(4-methyl)-piperidin-1-yl]-5-phenyl-pyrimidine

To a solution of 4-chloro-6-[(4-methyl)-piperidin-1-yl]-2-methyl-sulfony-5-phenyl-pyrimidine (1.0g, 2.7 mmol) in dimethylformamide (8ml) at room temperature was added potassium carbonate (0.76g, 5.47mmol). After the reaction mixture had been stirred at room temperature for 17.5 hours the reaction mixture was then diluted with water (70ml) and the resulting cloudy solution acidified to pH 1 by the addition of concentrated hydrochloric acid (4ml). The resulting white suspension was then stirred at room temperature for 2 hours. The suspension was then filtered, washed with water followed by hexane and dried in vacuo overnight. The crude product was recrystallized from methylene chloride/hexane to afford 0.71 g (79% yield) of the title compound as a white crystalline solid (melting point: 219-220°C (dec)).

## 24

## Example 41

Preparation of  
4-chloro-2-(N-cyano-N-methylamino)-6-[(4-methyl)-piperi-  
5 din-1-yl]-5-phenylpyrimidine

To a solution of 4-chloro-2-(N-cyanoamino)-6-[(4-methyl)-pi-  
peridin-1-yl]-5-phenylpyrimidine (0.1 g, 0.305mmol) in dimethyl-  
formamide (4ml) at room temperature was added water (2ml) follo-  
10 wed by potassium carbonate (0.084g, 0.61 mmol) and the resulting  
suspension was warmed gently to afford a clear solution. To the  
cooled solution was then added methyl iodide (0.076ml, 1.22mmol)  
and the reaction mixture stirred at room temperature for 2.5  
hours. The reaction was then quenched by the addition of satura-  
15 ted aqueous ammonium chloride solution (40ml). After adding ethyl  
acetate (40ml) the biphasic mixture was stirred for 5 minutes.  
The organic phase was then separated, washed with saturated brine  
(50ml), dried over magnesium sulfate and concentrated in vacuo to  
afford a yellow syrup. The crude product was chromatographed an  
20 silica gel eluting with 90:10 v/v hexane: ethyl acetate to afford  
0.09g (87% yield) of the title compound as a colorless syrup.

## Example 42

25 Preparation of  
2-(N-benzyl-N-cyano)-4-chloro-6-[(4-methyl)-piperi-  
din-1-yl]-5-phenylpyrimidine

To a solution of 4-chloro-2-(N-cyanoamino)-6-[(4-methyl)-piperi-  
30 din-1-yl]-5-phenyl-pyrimidine (0.37g, 1.13mmol) in dimethylform-  
amide (10ml) at room temperature was added water (3ml) and potas-  
sium carbonate (0.19g, 1.35mmol). To the resulting milky suspen-  
sion benzyl bromide (0.16ml, 1.35mmol) was added and stirred at  
room temperature for 18.75 hours before being quenched by the ad-  
35 dition of a saturated aqueous ammonium chloride solution (40ml).  
The mixture was then partitioned between ethyl acetate (75ml) and  
water (75ml), dried over magnesium sulfate and concentrated in  
vacuo to afford a yellow syrup. The crude product was chromato-  
graphed on silica gel eluting with 90:10 v/v hexane: ethyl ace-  
40 tate to afford 0.47g (100% yield) of the title compound as a  
white crystalline solid (melting point 98-100°C).



## 25

## Example 43

Alternative preparation of  
4-chloro-2-(N-cyano-N-methylamino)-6-[(4methyl)-piperi-  
5 din-1-yl]-5-phenylpyrimidine

To a solution of 4-chloro-6-[(4-methyl)-piperidin-1-yl]-2-methyl-  
sulfonyl-5-phenyl-pyrimidine (0.5g, 1.37mmol) in dimethylform-  
amide (6ml) was added potassium carbonate (0.38g, 2.73mmol) fol-  
10 lowed by methyl cyanamide (0.31 g, 5.47mmol). After stirring the  
reaction mixture at room temperature for 19 hours the reaction  
mixture was diluted with water (75ml), and extracted with ethyl  
acetate (75ml). The organic phase was washed with water (75ml),  
followed by saturated brine (75ml), dried over magnesium sulfate  
15 and concentrated in vacuo to afford a yellow syrup. The crude  
product was chromatographed on silica gel eluting with 90:10 v/v  
hexane: ethyl acetate to afford 0.39g (84% yield) of the title  
compound as a colorless syrup.

## 20 Example 44

Preparation of the starting material 4-chloro-6-[(4-methyl)-pi-  
peridin-1-yl]-2-methylsulfonyl-5-phenylpyrimidine

## 25 Step a: 5-Phenyl-2-methylthio-4,6(1H,5H)-pyrimidinedione

60.0 g (208 mmol) of ethyl 2-phenylmalonate and 19.0 g (249 mmol)  
of thiourea were heated at 150°C for 2.5 hours in 77 g (416 mmol)  
of tri-n-butylamine. The resultant ethanol was for the most part  
30 distilled off. After the reaction solution had cooled, 180 ml of  
an aqueous solution of 24.9 g (623 mmol) of NaOH were added to  
it. After adding 50 ml of cyclohexane and stirring for about  
30 min the aqueous phase was separated off, treated with 35.4 g  
(142 mmol) of methyl iodide and stirred at approximately 20 to  
35 25°C for about 16 h. After acidification with dilute HCl solution  
and stirring for about 30 min the precipitate was filtered off.  
After washing with water and drying, 16.7 g of the compound in  
the title (28 % of theoretical) were obtained in the form of  
white crystals.

40

## Step b: 4,6-Dichloro-5-phenyl-2-methylthiopyrimidine

A solution of 48.8 g (170 mmol) of the product from step A in  
200 ml of phosphoryl chloride to which 3 ml of dimethylformamide  
45 (DMF) had been added was refluxed for 40 hours. After distilling  
off most of the phosphoryl chloride and diluting the residue with  
ethyl acetate, water was added while stirring at 15 to 20°C. After

## 26

phase separation, the organic phase was washed with water and dilute NaHCO<sub>3</sub> solution, then dried and freed of solvent. 37.5 g of the compound in the title (68 % of theoretical) were obtained in the form of an oil which was employed in step C without further purification.

Step c: 6-Chloro-5-phenyl-4-[(4-methyl)piperidin-1-yl]-2-methylthiopyrimidine

10 A solution of 37.5 g (324 mmol) of the product from step B in 150 ml of anhydrous dichloromethane was treated with 24 g (406 mmol) of isopropylamine and stirred for five hours at about 20 to 25°C. The solvent was then distilled off, the residue taken up in ethyl acetate and washed with dilute HCl, water and dilute  
15 NaHCO<sub>3</sub> solution, then dried and freed of solvent. After chromatographing the residue on silica gel (cyclohexane/methyl tert-butyl ether 100:1 to 19:1) 13.4 g of the title compound (33 % of theoretical) were obtained in the form of colorless crystals which were employed in the next stage without further purification.

20

Step d: Preparation of 6-chloro-4-[(4-methyl)-piperidin-1-yl]-2-methyl-sulfonyl-5 phenylpyrimidine

A solution of 4-chloro-6-[(4-methyl)-piperidin-1-yl]-2-methyl-  
25 thio-5 phenylpyrimidine (17.19g, 51.5mmol) in methylene chloride (350ml) was cooled to 0°C. After adding 70% in chloroperbenzoic acid (25.4g, 103mmol) the reaction mixture was stirred at 0°C for 1 hour and at room temperature for 1.5 hours. The reaction mixture was then concentrated in vacuo to a small volume, diluted  
30 with ethyl acetate (400 ml), washed with 5% aqueous solution of sodium carbonate (3 x 300ml) and saturated brine (300ml), dried over magnesium sulfate and concentrated in vacuo to afford a white solid which was then recrystallized from ethyl acetate/hexane to afford 14.68g (78% yield) of the title compound as an  
35 off-white crystalline solid (melting point: 160-162°C).

Example 45

Preparation of the intermediate

40 4-chloro-6-(N-cyclopentyl)amino-5-(2-fluorophenyl)-2-methylthiopyrimidine

Step a: Preparation of 5-(2-fluorophenyl)-2-thiobarbituric acid

45 To absolute ethanol (200ml), sodium (3.62g, 157mmol) was added at room temperature under nitrogen atmosphere. The reaction mixture was stirred until all the sodium had reacted. A solution of

## 27

diethyl-(2-fluorophenyl)malonate (20g, 78.7mmol) in absolute ethanol (50ml) was then added followed by thiourea (8.38g, 110mmol). The reaction mixture was then refluxed under nitrogen atmosphere for 17 hours. The cooled reaction mixture was then poured into water (800ml), the reswiting mixture stirred for 15 minutes and extracted with diethyl ether (500ml). The organic phase was extracted with brine (150ml, 1/3 saturated) and the aqueous layers combined. Now concentrated hydrochloric acid (14ml) was added to the aqueous phase and the resulting white suspension was stirred gently for 1 hour. The suspension was filtered and the resulting solid washed with water, followed by diethyl ether and dried in vacuo for approximately 12 hours to afford 8.59g (46% yield) of the title compound as a white solid (melting point: >240°C).

15

Step b: Preparation of

4,6-dihydroxy-5-(2-fluorophenyl)-2-methylthiopyrimidine

To a mixture of 5-(2-fluorophenyl)-2-thiobarbituric acid (8.20g, 34.3mmol) and a 2.0M aqueous solution of sodium hydroxide (68.8ml, 13.8mmol) was added dropwise over 30 minutes dimethyl sulfate (4.348, 34.4mmol) at room temperature with stirring. The reaction mixture was stirred then for an additional 24 hours at room temperature. After washing with ethyl acetate (2 x 100ml) the aqueous phase was acidified to pH 1 by adding concentrated hydrochloric acid (8ml). The resulting white suspension was stirred for 30 minutes, filtered and the resulting white solid washed with water followed by hexane and dried under vacuum to afford 7.11 g of a white solid. Ethyl acetate (100ml) was added to the crude product and the resulting suspension refluxed while stirring for 15 minutes. The cooled suspension was then filtered and dried to afford 5.41 g (61% yield) of the title compound as a white solid (m. p. > 240°C).

35 Step c: Preparation of

4,6-dichloro-5-(2-fluorophenyl)-2-methylthiopyrimidine

To a suspension of 4,6-dihydroxy-5-(2-fluorophenyl)-2-methylthiopyrimidine (0.75g, 2.97mmol) in phosphorous oxychloride (7.5ml, 80.5mmol) was added tri-n-propylamine (1.24ml, 6.54mmol) at room temperature under nitrogen atmosphere. After refluxing the reaction mixture for 18 hours and cooling to room temperature the reaction mixture was concentrated in vacuo and the resulting dark brown residue was dissolved in a minimum amount of acetonitrile and added to water (75ml) under stirring. Ethyl acetate (75ml) was then added and the resulting biphasic mixture stirred vigorously for one hour. The organic phase was separated, washed with

## 28

2M aqueous hydrochloric acid (75ml), saturated aqueous sodium bicarbonate solution (2 x 75 ml) and saturated brine (75ml). After drying over magnesium sulfate the organic Phase was concentrated in vacuo to afford a light brown oil. The crude product 5 was chromatographed on silica gel eluting with 98:2 v/v hexane: ethyl acetate to afford 0.74g (86% yield) of the title compound as colorless crystals.

Step d: Preparation of 4-chloro-6-(N-cyclopentyl)amino-5-(2-fluorophenyl)-2-methylthiopyrimidine

To a solution of 4,6-dichloro-5-(2-fluorophenyl)-2-methylthiopyrimidine (0.74g, 256mmol) in methylene chloride (1 ml) at room temperature under nitrogen atmosphere was added cyclopentyl-amine 15 (1.01 ml, 10.24mmol) and the reaction mixture was stirred at room temperature for 15 hours. The reaction mixture was then diluted with 1:1 v/v diethyl ether ethyl acetate (75ml), washed with 1 M aqueous hydrochloric acid (2 x 75ml), saturated aqueous sodium bicarbonate solution (75ml) and saturated brine (75ml), dried 20 over magnesium sulfate and concentrated in vacuo to afford a colorless syrup. The crude product was chromatographed on silica gel eluting with 95:5 v/v hexane: ethyl acetate to afford 0.87g (100% yield) of the title compound as a white crystalline solid (melting point: 81-83°C).

25

## Example 46

## Preparation of the intermediate

4,6-dichloro-5-(2-chloro-6-fluorophenyl)-2-methylthiopyrimidine

30

Step a: Preparation of 4,6-dihydroxy-5-(2-chloro-5-fluorophenyl)-2-methylthiopyrimidine

A mixture of diethyl(2-chloro-6-fluorophenyl)malonate (12.01 g, 35 41.6mmol), thiourea (3.8g, 49.92mmol) and tributylamine (19.82ml, 83.2mmol) was stirred at 150°C under nitrogen atmosphere for 3 hours. The cooled reaction mixture was then partitioned between ethyl acetate (84ml) and 2.0M sodium hydroxide solution (83.2ml, 106mmol) with vigorous stirring for 15 minutes. The aqueous phase 40 was separated, dimethyl sulfate (5.258, 41.6mmol) added and the mixture stirred for approximately 12 hours at room temperature. Additional 5.0 sodium hydroxide solution (33.4ml, 166mmol) and dimethylsulfate (2.63g, 20.8mmol) were added and the mixture stirred for further 2 hours. The resulting suspension was then filtered, 45 the filtrate acidified to pH 1 by the addition of concentrated hydrochloric acid and stirred for 30 minutes. The resulting suspension was then filtered and the resulting white solid washed

29

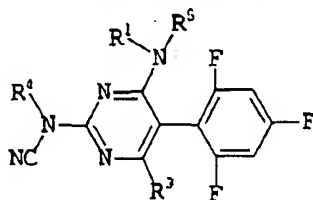
with water followed by hexane and dried under vacuum approximately 12 hours to afford 2.57g (22% yield) of the title compound as a white solid.

5 Step b: Preparation of 4,6-dichloro-5-(2-chloro-6-fluorophenyl)-2-methylthiopyrimidine

To a suspension of 4,6-dihydroxy-5-(2-chloro-6-fluorophenyl)-2-methylthiopyrimidine (2.57g, 8.96mmol) in phosphorous  
 10 oxychloride (25.7ml, 276mmol) was added tri-n-propylamine (3.75ml, 19.72mmol) at room temperature under nitrogen atmosphere. After refluxing the reaction mixture at 140°C for 40 hours and cooling to room temperature the reaction mixture was concentrated in vacuo to afford a black oil. The crude product was par-  
 15 titioned between ethyl acetate (250ml) and water (250ml) and the resulting biphasic mixture stirred vigorously for 15 minutes. The organic phase was separated, washed with 2M aqueous hydrochloric acid (2 x 250ml), saturated sodium bicarbonate solution (2x 250ml) and saturated brine (250ml). After drying over magnesium  
 20 sulfate the organic phase was concentrated in vacuo to afford 2.3g (79% yield) of the title compound as a dark brown solid.

Examples 47-49: Table III (synthesized analogously to Ex. 40-46)

25



IA

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Ex.	R <sup>1</sup>	R <sup>5</sup>	R <sup>4</sup>	melting point (°C)
47	CF <sub>3</sub> CH(CH <sub>3</sub> )	H	C <sub>6</sub> H <sub>5</sub> -CH <sub>2</sub>	178
48	(S)-CF <sub>3</sub> CH(CH <sub>3</sub> )	H	CH <sub>3</sub> O-C(=O)C(=CH <sub>2</sub> )CH <sub>2</sub>	120-123
49	CF <sub>3</sub> CH(CH <sub>3</sub> )	H	(CH <sub>3</sub> CH <sub>2</sub> O-C(=O)) <sub>2</sub> C(CH <sub>3</sub> )	178
50	CF <sub>3</sub> CH(CH <sub>3</sub> )	H	CH≡C-CH <sub>2</sub>	185-186
51	CF <sub>3</sub> CH(CH <sub>3</sub> )	H	thien-3-yl-CH <sub>2</sub>	68-72

40 Biological Investigations

A Determination of Minimum Inhibitory Concentration by Test Compounds in the Serial Dilution Test with *Pyricularia Oryzae*

45 The MIC (Minimum Inhibitory Concentration) value, which indicates the lowest concentration of the active ingredient in the growth medium which causes a total inhibition of mycelial growth, is

## 30

determined by serial dilution tests using Microtiter plates with 24 or 48 wells per plate. The dilution of the test compounds in the nutrient solution and the distribution to the wells is carried out by a TECAN RSP 5000 Robotic Sample Processor. The following test compound concentrations are used: 0.05, 0.10, 0.20, 0.39, 0.78, 1.56, 3.13, 6.25, 12.50, 25.00, 50.00 and 100.00 µg/ml. For preparation of the nutrient solution, V8 vegetable Juice (333 ml) is mixed with calcium carbonate (4.95 g), centrifuged, the supernatant (200 ml) diluted with water (800 ml) and 10 autoclaved at 121 °C for 30 min.

The inocula of *Pyricularia Oryzae* are added into the wells as spore suspensions (50 µl;  $5 \times 10^5$ /ml) or agar slices (6 mm) of an agar culture of the fungus.

15

After 6-12 days incubation at temperatures of 18 to 25°C, the MIC values are determined by visual inspection of the plates, as shown in Table IV.

20 Table IV

Example No.	MIC [µg/ml]
3	3.13
25 4	> 100
5	25
6	6.25
7	100

30 B Evaluation of In Vivo Fungicidal Activity of Test Compounds

Test compounds are dissolved in acetone and diluted with deionized water (95 parts water to 5 Parts acetone), containing 0.05% TWEEN 20®, a polyoxyethylene sorbitan monolaurate surfactant manufactured by Atlas Chemical Industries, to give a concentration of 200 ppm.

The plants are sprayed with the test solutions, dried and inoculated with fungi later the same day. When disease symptom development is optimal, the plants are rated for disease control according to the rating scale shown below. Each test contains inoculated treated plants, inoculated untreated plants and inoculated plants treated with reference fungicides. The data obtained are shown in Table V.

45

## 31

## RATING SCALE

Rating	Range % C ntrol
0	0
5 1	1-14
2	15-29
3	30-44
4	45-59
5	60-74
10 6	75-89
7	90-95
8	96-99
9	100

## 15 TARGETS

Symbol	Disease	Pathogen
AS	Apple Scab	<i>Venturia inaequalis</i>
RB	Rice Blast	<i>Pyricularia grisea</i> sp. <i>oryzae</i>
20 GDM	Grape downy mildew	<i>Uncinula necator</i>

Table V

	Example	AS	RB	GDM
25	2	0	0	0
	3	7	5	7
	4	5	3	3
	5	9	4	0
30	6	9	6	3

C Evaluation of In Vitro Fungicidal Activity against  
*Rhizoctonia solani*

35 Test compounds are dissolved in acetone to give a concentration of 10 ppm and added to individual cell walls (24-cell-well plates, Corning), which were previously filled with a suspension of ground fungal mycelium in a chemically defined growth medium. After 3-7 days of incubation, inhibition of mycelial growth is  
40 recorded using the following scale: The data obtained are shown in Table VI.

45

32

## RATING SCALE

Rating	Degree of Inhibition
0	None
5 3	slight
5	moderate
7	severe
9	complete

## 10 Table VI

Example	<i>Rhizoctonia solani</i> (Rice sheath blight)
1	7
15 4	7
5	0
6	0
7	0
8	7
20	

25

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